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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/503,596	02/11/2000	Mu-en Lee	05433-042001	6895

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/503,596	LEE ET AL.	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,5,6 and 9-12* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6 and 9-12* is/are rejected.

7)☒ Claim(s) *9* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1-3, 5, 6 and 9-12 are pending and currently under examination.

Claim Objections

Claim 9 is objected to because Claim 9 recites the limitation "wherein said antisense nucleic acid" in the first line. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejections - 35 USC § 112

The rejection of record of claim 1 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter is withdrawn in response to Applicant's arguments filed 04/18/2005.

The rejection of record of claims 1-3, 5-6 and 9-12 under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, is maintained. Applicant's arguments filed 04/18/2005 have been fully considered but are not persuasive.

Response to Applicant's Arguments

Applicants set forth the In re Wands factors and argue that in weighing all eight factors, the specification meets the standard for enablement for the full scope of the claimed invention. Applicant outlines each factor and a response to Applicant's arguments for each factor is discussed below:

Breadth of Claims, Nature of the invention and State of the Prior Art

Applicant argues that they have made an important contribution to the field of cardiovascular medicine and that by "[e]xploitation of this discovery according to the amended claims allows specific targeted inhibition of atherosclerotic lesion development by inhibiting macrophages from differentiating into foam cells." Applicant further argues that in light of the contribution of the claimed invention, the claims are not overly broad.

The claims are drawn to a method of inhibiting formation of an atherosclerotic lesion in a mammal or inhibiting differentiation of a macrophage into a foam cell by administration of an antisense to a whole organism, that is complementary to at least 10-100 nucleotides of the coding sequence of SEQ ID NO: 2, and further that reduces expression of AFABP. The nature of the invention is drawn broadly to administering an antisense to a *whole organism* and despite the contribution to the field of cardiovascular medicine, does overcome the unpredictability of administration of antisense compounds to whole organisms

As cited in the previous Office action filed 11/23/2001, Branch stresses that the state of the antisense art is very unpredictable "...it is very hard to predict what portions of an RNA

molecule will be accessible in vivo, effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (see page 49).

Therefore, the claims and the specification as filed do not provide guidance to allow one skilled in the art to practice the invention without a substantial amount of trial and error experimentation, an amount considered undue and not routine.

Level of one of ordinary skill in the art

Applicants argue that undue experimentation would not be required because "armed with the information provided in the specification regarding which compounds to administer, how to administer, and what kind of cells to contact, those skilled in the art would readily be able to carryout the invention as now claimed."

As stated in the prior Office action filed 10/18/2004, although Applicants have provided target sequences, an antisense sequence and methods to increase the stability of antisense oligonucleotides, the specification as filed does not teach how to administer the antisense to whole organisms to inhibit atherosclerotic lesions as claimed. In light of the conclusions on the state of the art, as stated by Branch above, to practice the claimed invention, one of skill in the art would have to *de novo* determine; the stability of the antisense molecule *in vivo*, delivery of the antisense molecule to the whole organism, specificity to the target tissue *in vivo*, dosage and toxicity *in vivo*, and entry of the molecule into the cell *in vivo* and the effective action therein. Without further guidance, one of skill in the art would have to engage in a substantial amount of trial and error experimentation, an amount considered undue and not routine, to practice the instantly claimed invention.

Predictability in the art

Applicants argue that the field of *in vivo* antisense applications is not highly unpredictable because "[a]lthough antisense methods may require further experimentation to optimize the desired result of reduced expression of a target gene, the methodology is well established and well accepted by the scientific and medical community." Applicants cite a review by Hogrefe wherein Hogrefe concludes that "...*in vivo* delivery does not appear to be a problem..." since"... all of the oligonucleotides in clinical trials are administered as saline solutions without delivery vehicles."

The only evidence that Hogrefe has to support his statement that "*in vivo* delivery does not appear to be a problem" is a table showing the current oligonucleotides that are in clinical trials. Hogrefe even admits his statement is "...controversial." The mere fact that an oligonucleotide has entered clinical trials does not overcome the unpredictability in the art for therapeutic *in vivo* applications using antisense compounds. It must be noted from the review by Hogrefe, only one antisense drug is manufactured for commercial purposes. As evidenced by post filing art, "...antisense-based therapeutics are far from being an established reality." (see abstract, Schiavone et al. Current Pharmaceutical Design, 2004).

Applicants have not provided any guidance in the specification that treatment of cells, *in vitro*, with an antisense targeted to a gene encoding AFABP would prevent atherosclerotic lesion formation. Furthermore, as stated in the Office action mailed 8/14/02, even with *in vitro* experimentation, it is not predictable that an antisense which inhibits a target gene in cells in culture will function equivalently in a *whole organism* in view of the numerous unpredictable considerations found in a whole organisms. As cited previously in the above Office action,

Crooke supports the difficulties of interpreting *in vitro* cellular assays and Schiavone et al. agrees and states, "[d]espite the success obtained in *in vitro* studies, the development of antisense drugs has met obstacles in the clinical field where results are far from satisfactory."

Additionally, the specification does not teach (1) stability of the antisense molecule *in vivo*, (2) delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. There is no guidance in the specification as filed that teaches how the claimed antisense compounds enter the human macrophage cell, inhibit the expression of AFABP, prevent the human macrophage from differentiating into a foam cell and ultimately inhibit atherosclerotic lesions.

Applicants have admitted above that the antisense methods may require further experimentation to optimize the desired result of reduced expression of a target gene, namely AFABP, and given the lack of guidance in the specification, this further experimentation would require one skilled in the art to engage in a substantial amount of trial and error experimentation, an amount that would be considered undue and not routine.

Amount of direction or guidance presented and Presence or absence of working examples

Applicants argue "adequate guidance is provided in the specification of the application to allow one skilled in the art to identify compounds that inhibit the expression of AFABP and carry out the claimed invention without having to resort to 'trial and error experimentation'." Applicants further argue that "little or no experimentation is required to determine which compounds to administer" because the specification provides assays that can be used for *in vitro*

testing for compounds that are complementary to AFABP mRNA. Further Applicants argue that "since extensive guidance is provided regarding modes of administration, minimal experimentation would be required to determine the concentration or dose of the compound to be administered, such determinations are routine in the art and would not require undue experimentation."

Although Applicants provide an assay to measure the differentiation of macrophages into foam cells after treatment with an antisense compound targeted to a gene encoding AFABP, this assay is only prophetic. Furthermore, as stated above, it is not predictable that an antisense which inhibits a target gene in cells in culture will function equivalently in a *whole organism* in view of the numerous unpredictable considerations found in a whole organisms.

Additionally, although Applicants have provided modes of administration of an antisense compound to a mouse and provided an art-recognized mouse model of vascular disease, the teachings of the modes of administration of an antisense compound and the mouse model do not provide adequate guidance for determining concentration, toxicity, specificity of binding and the rate of degradation, such that any kind of AFABP inhibition *in vivo* could be predicted, and further that inhibition of atherosclerotic lesion formation would be provided.

As stated in the previous Office action filed 10/18/2005, the knock-out model does not teach how to deliver the claimed antisense compound to the macrophage cells *in vivo* and how this antisense compound will inhibit the expression of the AFABP, which will then lead to a decrease in atherosclerotic lesions. Although Applicant has provided evidence, via the knock-out mouse model, that there is a correlation between decreased levels of AFABP and decreased atherosclerotic lesions, the knock-out mouse model does not provide guidance on how

administration of an antisense targeted to a gene encoding AFABP would lead to decreased atherosclerotic lesions. Because there is no specific guidance taught by the knock-out mouse model, the specification as filed or the prior art, one skilled in the art would have to engage in and practice trial and error experimentation to discover antisense that are able to target AFABP, in a whole animal, in such a manner as to provide the claimed functions, namely inhibition of atherosclerotic lesions.

Therefore, in considering the sum total of the evidence, they do not teach how the claimed antisense compounds enter the human macrophage cell, inhibit the expression of AFABP, prevent the human macrophage from differentiating into a foam cell and ultimately inhibit atherosclerotic lesions. Thus, the specifications as filed do not provide guidance on how to overcome the high level of unpredictability in the art for design of any such antisense therapeutic compound.

THIS ACTION IS FINAL.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-3111. The examiner can normally be reached Monday thru Friday between 7-4 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached at 571-272-0811. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

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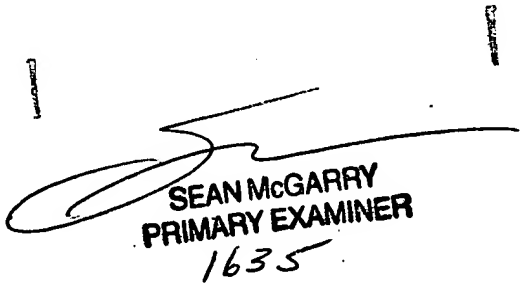

Kimberly Chong
Examiner
Art Unit 1635